

Atezolizumab-associated encephalitis in metastatic breast cancer: A case report

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Abstract. Immune checkpoint inhibitors have been critical in the treatment of advanced malignancies in recent years. Encephalitis caused by atezolizumab is an uncommon immune-related adverse event. The case of a 65-year-old female diagnosed with encephalitis closely associated with atezolizumab medication for metastatic advanced breast cancer is presented in the current study. Following a fourth atezolizumab dose 10 days previously, the patient fell into a deep coma. Initial brain magnetic resonance imaging revealed multiple patchy T2 hyperintensities in the bilateral cerebellar hemisphere, vermis of the cerebellum, bilateral frontal lobe, temporal lobe, parietal lobe and occipital cortex. Meanwhile, there were aberrant signs on diffusion-weighted imaging. The diagnosis of atezolizumab-induced encephalitis seemed probable after ruling out other possible causes of encephalitis. Subsequently, the condition of the patient worsened and there were indications of cardiac and respiratory arrest. Chest compressions were provided immediately, as well as a balloon mask for assisted ventilation, a medication boost, stimulated breathing and other symptomatic therapy. The patient's vital signs temporarily stabilised after this series of rescue measures. The patient refused further therapy and insisted on being discharged, and died a few days after being discharged from

the hospital. In this case, the patient's encephalitis symptoms associated with atezolizumab were not as typical as previously documented. The patient's condition swiftly deteriorated to heartbeat apnea, and steroid pulse therapy was not received in a timely manner, resulting in an unfavourable outcome.

Introduction

Immune checkpoint inhibitors (ICIs), which can block the cytotoxic T lymphocyte-associated protein 4 (CTLA-4) or programmed cell death 1 (PD-1) pathways, have recently played an important role in the treatment of advanced malignancies (1,2). Atezolizumab, an ICI that inhibits PD-L1 to promote endogenous antitumour immunity, has been utilised in the treatment of malignant tumours. However, as ICIs have become more commonly used, different autoimmune side effects known as immune-related adverse events (irAEs) have become a rising source of concern. Neurological irAEs are seldom documented, and extensive studies show that the prevalence of neurological AEs caused by immune checkpoint inhibitor medication is ~1% (3). Neurological irAEs can cause central and peripheral nervous system damage, resulting in encephalopathy/encephalitis, central nervous system (CNS) demyelination, aseptic meningitis, transverse myelitis, posterior reversible leukoencephalopathy syndrome, peripheral neuropathy, myasthenia-like syndrome, Guillain-Barré syndrome-like illness and myopathy (4,5). Encephalitis is estimated to occur in 0.1-0.2% of patients treated with ICIs (6). To the best of our knowledge, atezolizumab-associated encephalitis has been reported in bladder cancer, cervical cancer, lung cancer, hepatocellular carcinoma and breast cancer (7-15). It is clinically characterized by seizures, confusion, altered behavior, headaches and alterations of consciousness (16). Brain MRI revealed T2 hyperintensities with or without contrast enhancement. Lumbar puncture frequently revealed lymphocytic and leucocytic pleiocytosis, while cytopathology was negative (17). Patients with ICI-related encephalitis generally recovered completely or partially after corticosteroid therapy. The current study presents a case of irAEs in the CNS. To the best of our knowledge, this is the first case of encephalitis in China closely linked to atezolizumab.

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Case report

In May 2019, a 65-year-old female was admitted to Boai Hospital of Zhongshan (Zhongshan, China) with redness, swelling, heat, and pain in the left breast for one month. The patient was diagnosed with infiltrating ductal carcinoma of the left breast via fine-needle aspiration. No metastatic signs were present at first, and stage II disease (18) was indicated from the histological analysis. Six sessions of chemotherapy were administered, the first four of which consisted of epirubicin and cyclophosphamide, followed by two treatments of docetaxel. As the patient did not respond well to docetaxel, the chemotherapy regimen was modified to paclitaxel and carboplatin. The breast tumour was significantly decreased in size after a further three lines of treatment. Due to grade IV myelosuppression, the fourth round of chemotherapy was not finished.

In December 2019, the patient was scheduled for a subcutaneous mastectomy with axillary and subclavian lymph node dissection. Pathological findings revealed multiple metastases to the left axillary lymph nodes and latissimus dorsi. A diagnosis of triple-negative breast carcinoma (rT4N0M1) (19) was made based on the immunohistochemistry results. The patient refused the chemotherapy regimens recommended by the doctors and instead received radiotherapy. After 6 months, the patient was diagnosed with a metastatic tumour of the 9th thoracic vertebrae and left anterior chest using integrated positron emission tomography and computed tomography, indicating progression of the disease. At that time, PDL-1 testing was negative. To inhibit the progression of the tumor, doctors decided to begin treatment with atezolizumab at 1,200 mg in conjunction with paclitaxel at 200 mg per dose. Chemotherapy had to be put on hold during treatment due to a lung infection and a urinary tract infection.

The patient became somnolent 10 days after taking a fourth dose of atezolizumab and was admitted to Guangdong Provincial Hospital of Chinese Medicine (Guangzhou, China). The neurological examination revealed a disruption in consciousness (Glasgow Coma Scale E1V1M3) (19) but no other abnormal findings. MRI of the brain (Fig. 1) revealed multiple patchy T2 hyperintensities in the bilateral cerebellar hemisphere, vermis of the cerebellum, bilateral frontal lobe, temporal lobe, parietal lobe and occipital cortex. These lesions exhibited hyperintense signal on diffusion-weighted imaging, which was suggestive of intracellular edema. However, when doctors reviewed the previous MRI report from 23 days before, no abnormal signals were found in the brain parenchyma, and the size and shape of each ventricle and cistern was normal (Fig. 2). The appearance of these new lesions confirmed the deterioration of the patient's condition. At that time, the possibility of immune-related encephalitis was considered first, so the patient was administered an intravenous infusion of 10 ml dexamethasone. However, brain metastases and paraneoplastic neurological syndrome were not ruled out. As a result, a lumbar puncture, cerebrospinal fluid (CSF) culture and cytology, viral serologies of the blood and cerebrospinal fluid, and antineuronal antibody detection were all necessary for the diagnosis. However, the patient's physical health rapidly deteriorated and she eventually fell into a deep coma with no response to any stimulus. The heart rate was 140 (normal ranges, 60-100) beats/min and the blood pressure was 150/110 (normal range, 90-140/60-90) mmHg. At that time, the workup

revealed a white blood cell count of 3.87 (normal range, 3.5-9.5) $\times 10^9/l$, a lymphocyte count of 0.39 (normal range, 1.1-3.2) $\times 10^9/l$, a red blood cell count of 3.63 (normal range, 3.8-5.1) $\times 10^9/l$, a haemoglobin level of 88 (normal range, 115-150) g/l, a D-dimer level of 7.84 (normal range, 0-0.5) mg/l and a fibrinogen degradation product of 25.52 (normal range, 0-5) mg/l. Importantly, blood oxygen saturation declined to 83% (normal range, 91.9-99%). The partial pressures of oxygen and carbon dioxide were 54.1 (normal range, 80-100) and 53.8 (normal range, 35-45) mmHg, respectively, indicating type 2 respiratory failure. Ventilation with a non-invasive ventilator was provided; however, the patient's condition worsened and cardiac and respiratory arrest occurred. Doctors performed chest compressions, airbag mask-assisted ventilation, medication boosting, stimulated breathing and other symptomatic treatments. The patient and family refused endotracheal intubation or being transferred to the intensive care unit. After a temporary stabilization of vital signs as a result of a series of rescue measures, the patient was discharged. A telephone follow-up conversation later revealed that the patient had died a few days after being discharged from the hospital.

Discussion

Immune checkpoint inhibitors have a well-documented history of causing neurological adverse results, with an incidence ranging from 3.8-6.1% (16,20). The beginning of neurological irAEs ranges from 6-13 weeks after the initiation of ICI, but they can occur at any time during treatment and even after termination (10,21). It is possible that the central and/or peripheral nervous systems are affected. According to the European Society for Medical Oncology clinical practice guidelines recommended, symptoms of irAEs may be divided into four grades (22). Asthenia, headaches, dizziness, paresthesia or dysgeusia are common symptoms of grades 1 and 2 (22,23). Myasthenia gravis, Guillain-Barré syndrome, chronic inflammatory polyneuropathy, myelitis, aseptic meningitis, encephalitis and posterior-reversible encephalopathy are the more common authentic neurological syndromes in grades 3 and 4 (22,23). Although neurological irAEs are uncommon, they often manifest as serious diseases with a high fatality rate (24). Encephalitis caused by atezolizumab has only been recorded in a few cases as an irAE. To the best of our knowledge, only 9 cases have been reported (7-15). The main information for these cases is shown in Table I.

Table I reveals that atezolizumab-associated encephalitis has been described in bladder cancer, cervical cancer, lung cancer, hepatocellular carcinoma and breast cancer. Furthermore, 3 cases were noted in an atezolizumab clinical study in triple-negative breast cancer (25). The current case is the fifth case associated with breast cancer.

It is possible to draw conclusions based on the clinical symptoms of those cases mentioned in the Table I. First, symptoms of neurological irAEs appeared ~2 weeks after the patients received their first dose of atezolizumab in all cases. Second, the predominant symptoms were a high fever and a disturbance of consciousness. Third, MRI revealed encephalitis symptoms. CSF investigation revealed encephalitis due to an increase in the number of leucocytes, lymphocytes and protein. Furthermore, CSF was negative for bacterial

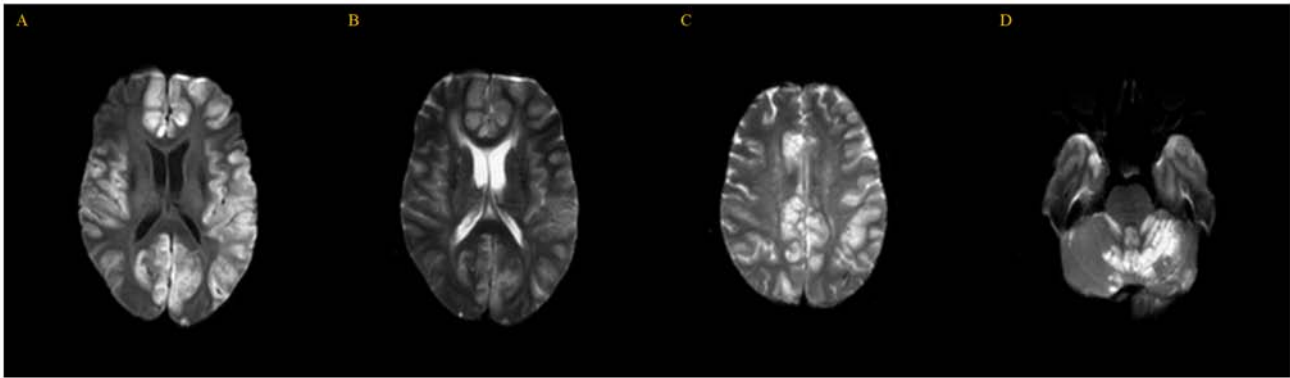


Figure 1. Brain MRI at 10 days after the patient received the fourth atezolizumab dose. MRI showed multiple hyperintense signals in (A) the bilateral frontal lobe and (D) bilateral cerebellar hemisphere and cerebellar vermis on diffusion-weighted imaging. It also revealed hyperintense signal in (B) the temporal lobe and (C) parietal lobe and occipital cortex on T2WI, which indicated intracellular edema. MRI, magnetic resonance imaging; T2WI, T2-weighted imaging.

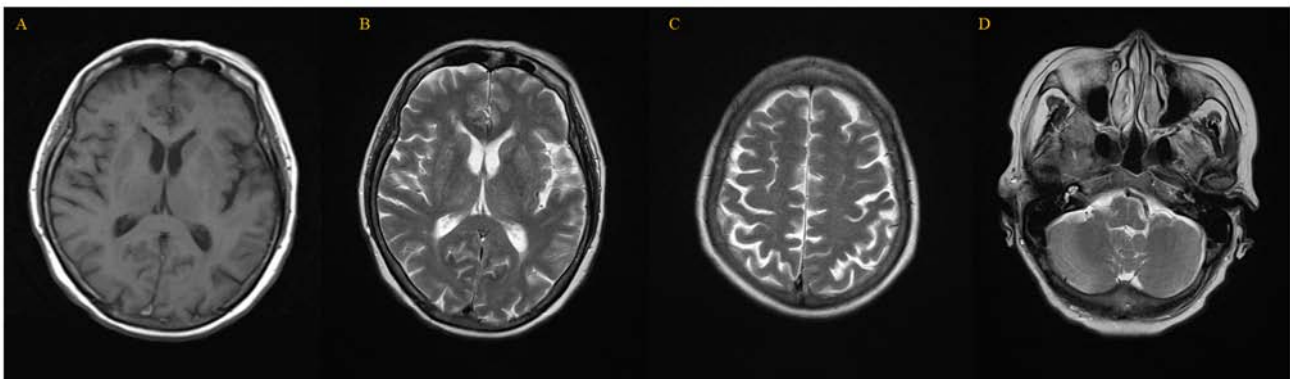


Figure 2. Brain MRI at 13 days before the patient received the fourth atezolizumab dose. No basal ganglia lesions were observed on (A) T1WI and (B) T2WI. No abnormal signal was observed in the (C) bilateral frontal and temporal lobes and (D) cerebellum on T2WI. MRI, magnetic resonance imaging; T1WI, T1-weighted imaging.

and fungal cultures, as were other associated autoantibodies. Consequently, atezolizumab-associated encephalitis was discovered after ruling out other possible causes of encephalitis using MRI, CSF analysis and autoantibody assays. Fourth, in these cases, steroid pulse therapy has been shown to be helpful. Since atezolizumab-associated encephalitis is rare, it may be seen from the existing case reports and clinical guidelines that the most direct objective index of this rare encephalitis for diagnosis is still uncertain (17). Clinicians rely on an exclusive diagnosis, i.e., a diagnosis of atezolizumab-associated encephalitis after excluding other causes of encephalitis, including infectious, toxic and metabolic causes. Therefore, in the diagnosis, the results of CSF-related examinations are necessary (10). In terms of treatment, timely administration of steroids may prevent rapid deterioration of patients (16).

In contrast to those previously described cases of atezolizumab-associated encephalitis (Table I), the patient in the present case displayed distinct clinical manifestations. Fig. 3 shows the patient's overall course of treatment, particularly the duration of atezolizumab treatment. No discomfort was noted after the first dose of atezolizumab and there was no sign of prodromal infection based on the results of an MRI and a chest X-ray prior to admission. However, encephalitis developed 10 days after the fourth dose of atezolizumab therapy. An immediate loss of consciousness, with multiple T2 hyperintensities in

the initial brain MRI, indicated encephalitis. This outbreak of encephalitis affected a wide area, including bilateral cerebellar hemispheres, vermis, bilateral frontal lobe, temporal lobe, parietal lobe, occipital cortex and medulla oblongata, resulting in loss of consciousness and respiratory failure. Although physicians fully explained the patient's condition and treatment plans to the family, they refused to allow further treatments or a full inspection, including the CSF and autoantibody examinations, which accounted for the difficulty in verifying the diagnosis. After ruling out other possible causes, the physicians highly suspected that the encephalitis was caused by atezolizumab.

The precise mechanism of neurological irAEs has not yet been established. In ICI therapies, monoclonal antibodies are employed to block the expression of proteins [CTLA4, PD-1 and programmed death-ligand 1 (PD-L1)] and thereby increase T-cell activation against tumours (5). The onset of immune-associated AEs may be more closely associated with anti-PD-1 and anti-PD-L1 antibody responses than with anti-CTLA-4 antibody responses (26). A post-hoc analysis of a phase II trial assessing the efficacy of ipilimumab as a combination with chemotherapy in the treatment of metastatic small-cell lung cancer indicated that the presence of antineuronal antibodies was associated with more irAEs and particularly neurological toxicity (27).

ICI-mediated encephalitis is a medical emergency and a diagnosis by exclusion; it can be present in a variety of clinical

Table I. Main information on cases of atezolizumab-associated encephalitis.

First author, year	Patient			Manifestation of encephalitis				Interventions	Outcome	(Refs.)
	Age, years	Sex	Type of malignant tumour	Time of onset	Main symptoms	MRI	CSF			
Levine <i>et al</i> , 2017	59	Female	Metastatic bladder cancer	12 days after first dose	Confusion, fatigue, spastic tremors and vomiting	Left frontal lobe mildly enhancing lesion	Glucose: 80 mg/dl; protein: 100 mg/dl; negative paraneoplastic tests	Steroids	Symptoms improved, with upper extremity weakness left	(7)
Laserna <i>et al</i> , 2018	53	Female	Cervical squamous cell carcinoma	13 days after first dose	Altered mental status and headache	Diffuse leptomeningeal enhancement	Protein: >600 mg/ dl; glucose: 92 mg/ dl; negative CSF cultures	Steroids	Symptoms improved, with muscle weakness left	(8)
Arakawa <i>et al</i> , 2018	78	Male	Metastatic lung cancer	13 days after first dose	Confusion and fever	Unmentioned	Cell count: 139/ μ l; protein 132 mg/dl	Steroids	Recovered	(9)
Robert <i>et al</i> , 2020	48/F	Female	Metastatic lung adenocarcinoma	13 days after first dose	Fever, temporospatial disorientation, memory impairment and aphasia	Pachymeningitis and leptomeningitis.	Elevated protein	Steroids	Recovered	(10)
Yamaguchi <i>et al</i> , 2020	56	Female	Metastatic lung adenocarcinoma	17 days after first dose	Fever, consciousness disorder and motor aphasia	Unmentioned	Cell count: 20/ μ l; protein: 166 mg/ glucose: 73 mg/dl; interleukin: 682.9 pg/ml	Steroids	Recovered	(11)
Tatsumi <i>et al</i> , 2020	76	Male	Small cell lung cancer	5 months after first dose	Irritability and forgetfulness	T2-hyper- intensity in the bilateral striatum.	A high titer of anti-CRMP5 antibody	Steroids	Recovered	(12)

Table I. Continued.

First author, year	Patient			Manifestation of encephalitis				Interventions	Outcome	(Refs.)
	Age, years	Sex	Type of malignant tumour	Time of onset	Main symptoms	MRI	CSF			
Nader <i>et al</i> , 2021	38	Female	Metastatic triple-negative breast cancer	10 days after first dose	Fever, seizures and somnolence	Moderate diffuse leptomeningeal enhancement bilaterally	No malignant cells and negative CSF cultures	Steroids	Remained stable for ~1 year, passed away after 5 years due to an infection	(13)
Özdırık <i>et al</i> , 2021	70	Female	Multifocal hepatocellular carcinoma	10 days after first dose	Impaired cognition and language, somnolence, emesis and dyspnea	Unmentioned	Leucocyte count: 179/ml; protein: 5,494 mg/dl; negative CSF cultures	Steroids and plasma-pheresis	Died due to multi-organ failure	(14)
Nishijima <i>et al</i> , 2022	72	Female	Non-small cell lung cancer	Uncertain	Gait disturbance and mild disturbance of consciousness	Symmetrical high signal in the thalamus bilaterally	Unmentioned	Steroids and IVIG	Died due to aspiration pneumonia	(15)
Chen <i>et al</i> , 2022	65	Female	Metastatic triple-negative breast cancer	10 days after fourth dose	Coma and respiratory failure	T2 and DWI hyperintense signals in the bilateral cerebellar hemisphere, vermis of the cerebellum, bilateral frontal lobe, temporal lobe, parietal lobe and occipital cortex	None	Steroids	Dead	Present case

MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; IVIG, intravenous immune globulin; CRMP5, collapsin response mediator protein 5. sT2, T2 weighted imaging. DWI, diffusion-weighted imaging.

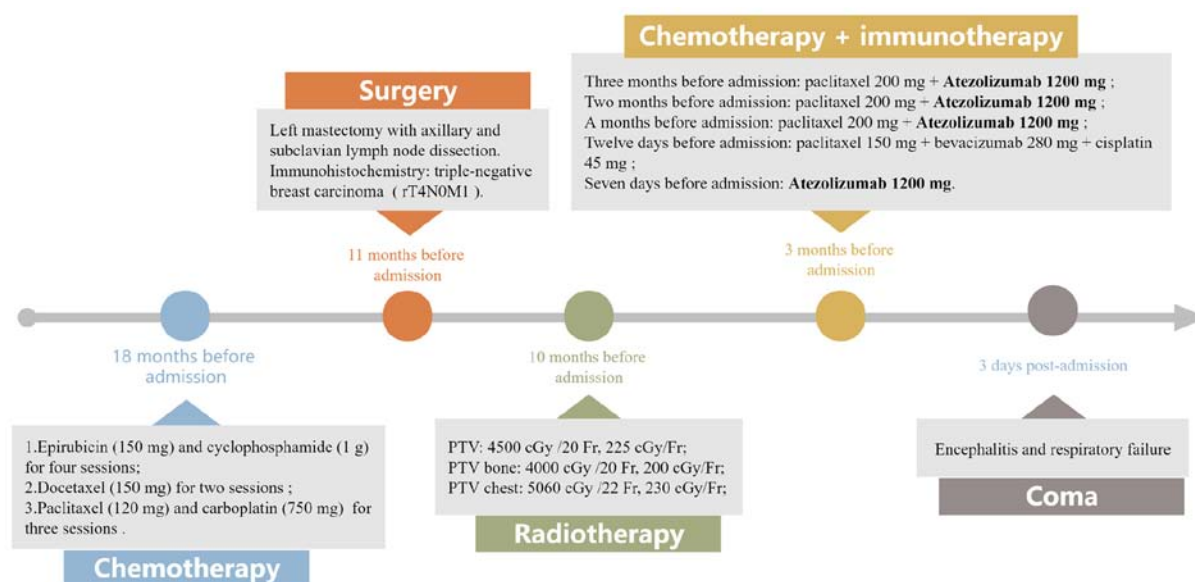


Figure 3. Timeline of treatments. PTV, planning target volume.

manifestations, making diagnosis and therapy problematic. The diagnosis of ICI-mediated neurotoxicities is difficult due to the rich variety of differential diagnoses, which includes tumour progression, paraneoplastic neurologic disorders, metabolic derangements, infections and complications associated with concurrent treatment modalities (21). The present study emphasizes the important relevance of MRI in the early detection of ICI-related encephalitis. MRI is considered to be the one of the accurate and non-invasive tests available to evaluate the changes of lesions in the brain. MRI is also a powerful basis for clinicians to diagnose and make medical decisions in such cases. Complementary examinations are also essential, including a full biological assessment, viral serologies in the blood and cerebrospinal fluid and antineuronal antibody determination (10). Although they were invasive tests and could not give immediate results, the lack of additional examinations to support the diagnosis was considered as a limitation in the present case.

When atezolizumab-associated encephalitis occurs, steroid pulse treatment is used to alleviate brain inflammation, according to current irAE care guidelines (16). After visiting a neurologist, serious cases should be treated with intravenous immunoglobulin and plasmapheresis (28). If the patient and family members in the present study had agreed to active treatment, the patient's results would likely have been completely different. The doctors might have been able to confirm the diagnosis and steroid pulse treatment could have been administered to the patient. Therefore, the manner in which rare ICI-mediated encephalitis can be accurately identified in clinical practice and how to make the most beneficial medical decisions for patients are directions for our future efforts.

In conclusion, as the application of ICIs for treating diverse types of malignancies expands, the occurrence of clinical irAEs will surely increase. Despite an uncertain cause and the lack of focused treatment for atezolizumab-associated encephalitis, doctors are obliged to constantly update their working knowledge in order to appropriately diagnose and manage these cases. Prompt identification and treatment are essential for successful management. Therefore, it is very

important to consult experts in order to clarify a diagnosis in a timely manner. Physicians are obliged to decide the optimal measures after carefully examining the severity of the irAEs and the condition of the patient. Since irAEs can affect different organs, a collaborative approach connecting with experts from multiple fields is useful.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

GC was responsible for the study conception, reviewed the literature and drafted the manuscript. CZ and JL confirmed the authenticity of all the raw data analyzed and interpreted the data and edited the manuscript. ZL obtained medical images (MRI scans) and analyzed patient data. YZ and HZ contributed to the study conception, overall design and quality control. All authors reviewed the manuscript critically and approved the submission.

Ethics approval and consent to participate

This case report was approved by the Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine (Guangzhou, China).

Patient consent for publication

The patient's family provided oral consent for the article to be published. The Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine (Guangzhou, China) approved that oral consent was sufficient in this case report.

Competing interests

The authors declare that they have no competing interests.

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